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Disease Extent at Secondary Cytoreductive Surgery is Predictive of Progression-free and Overall Survival in Advanced Stage Ovarian Cancer: an NRG Oncology/Gynecologic Oncology Group study

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Abstract

Purpose—GOG 152 was a randomized trial of secondary cytoreductive surgery (SCS) in patients with suboptimal residual disease (residual tumor nodule >1 cm in greatest diameter) following primary cytoreductive surgery for advanced stage ovarian cancer. The current analysis was undertaken to evaluate the impact of disease findings at SCS on progression-free survival (PFS) and overall survival (OS).

Methods—Among the 550 patients enrolled on GOG-152, two-hundred-sixteen patients were randomly assigned following 3 cycles of cisplatin and paclitaxel to receive SCS. In 15 patients (7%) surgery was declined or contraindicated. In the remaining 201 patients the operative and pathology reports were utilized to classify their disease status at the beginning of SCS as; no gross

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CONFLICT OF INTEREST

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disease/microscopically negative N= 40 (19.9%), no gross disease/microscopically positive N= 8 (4.0%), and gross disease N=153 (76.1%).

Results—The median PFS for patients with no gross disease/microscopically negative was 16.1 months, no gross disease/microscopically positive was 13.5 months and for gross disease was 11.7 months, p=0.002. The median OS for patients with no gross disease/microscopically negative was 51.5 months, no gross disease/microscopically positive was 42.6 months and for gross disease was 34.9 months, p=0.018.

Conclusion—Although as previously reported SCS did not change PFS or OS, for those who underwent the procedure, their operative and pathologic findings were predictive of PFS and OS. Surgical/pathological residual disease is a biomarker of response to chemotherapy and predictive of PFS and OS.

Keywords

Pathologic complete response; secondary cytoreduction

INTRODUCTION

The approval of new oncology therapeutics is time intensive and ultimately requires a phase III randomized trial testing a new regimen against standard therapy [1]. However, years of preclinical and early clinical trial development are required before a Phase III randomized trial can commence. Additionally, the conduct of a Phase III randomized trial is lengthy and includes; patient recruitment, completion of a therapeutic intervention and close observation for clinical events. For certain cancers with a long median survival, such as breast or ovarian cancer, years of observation are often necessary for event outcomes (progression and death) to occur. While the current drug approval “identity to registration” paradigm is effective, collectively, the approval of a new oncology therapeutic may take a decade or more.

A surrogate endpoint of survival that could be identified early in the course of disease treatment could potentially shorten approval of new oncology therapeutics. A pathologic complete response has been identified as a biomarker of response to chemotherapy and is predictive of progression-free survival (PFS) and overall survival (OS) in multiple tumor types [2,3,4]. In breast cancer, pathologic complete response following neoadjuvant chemotherapy has been utilized for “accelerated” approval of pertuzumab although final survival will still need to be demonstrated for “regular” approval [5]. The benefit of accelerated approval is that it allows earlier availability of therapeutic agents for cancer patients. In ovarian cancer data regarding pathologic complete response (CR) rates following induction chemotherapy are lacking. In a large Italian retrospective multicenter study of 322 patients treated with neoadjuvant chemotherapy and interval debulking surgery the pathologic CR was 6.5% [6]. For patients with a pathologic CR the median PFS was 36 month and median OS was 72 months, compared to PFS and OS of 16 months and 38 months for microscopic partial response (PR) and 13 months and 29 months for macroscopic PR patients. However, the number of the courses of chemotherapy before interval debulking surgery varied from 4 to 6 and the regimens utilized varied but were all carboplatin based. More recently the results of the Chorus trial have been presented with 4% of the patients

undergoing 3 cycles of platinum-based chemotherapy and interval debulking surgery having no evidence of residual disease.[7] However, the outcome of this patient population has not been defined.

The amount of residual disease following primary debulking surgery is associated with PFS and OS [8]. Hoskins and McGuire evaluating Gynecologic Oncology Group (GOG) data established the optimal residual disease diameter as 1 cm or less and suboptimal as more than 1 cm [9]. In an effort to optimize residual disease secondary cytoreductive surgery has been used in patients who have undergone suboptimal primary surgery. GOG-152 was a randomized trial evaluating the utility of secondary cytoreductive surgery for patients with suboptimal primary debulking following 3 cycles of chemotherapy with cisplatin and paclitaxel [10]. This trial, which was previously reported, demonstrated no improvement for patients who underwent secondary cytoreductive surgery. The purpose of the current study was to evaluate the association between surgical pathologic findings of patients who underwent secondary cytoreductive surgery (SCS) and survival outcomes.

METHODS

The methodology for this study has previously been published in detail [9]. Briefly, from June 1994 through January 2001, 550 patients who had advanced ovarian cancer and residual tumor exceeding 1 cm in diameter after primary surgery, were enrolled and 424 eligible were randomized; 216 to chemotherapy plus SCS and 208 to chemotherapy alone. In 15 patients (7%) randomized to SCS, surgery was declined or contraindicated. The remaining 201 patients who received chemotherapy and SCS are the subject of this study. All patients had surgical report forms which documented at least 55 potential sites of residual intra-abdominal disease following their primary and secondary cytoreductive procedures. Secondary cytoreductive surgery was prescribed to be performed after the third course of chemotherapy as soon as nadir counts permitted but must have been performed within 6 weeks of the third course of chemotherapy. Secondary cytoreductive surgery involved an abdominal incision adequate to explore the entire abdominal cavity. All peritoneal surfaces including the undersurface of both diaphragms and the serosa and mesentery of the entire GI tract were to be visualized and palpated. Careful inspection and removal of at least the infracolic omentum was mandated as well as extra fascial hysterectomy and bilateral salpingo-oophorectomy if not performed at the primary cytoreductive procedure. All gross residual disease identified was to be resected.

Disease status at secondary cytoreductive surgery was evaluated by operative and pathologic reports. Patients disease status at the beginning of their SCS was classified as one of 3 groups; pathologic CR: those having no gross residual disease and no microscopic disease, pathologic PR: those having no gross residual disease but microscopic disease, and gross disease: those having gross residual disease.

In the statistical analysis, categorical variables were compared between the patient subgroups by the Pearson chi-square test [11], and continuous variables by the Kruskal–Wallis test [12]. Progression-free and overall survival was estimated using the Kaplan–Meier method [13], and differences between groups evaluated by the log-rank test. All statistical

tests were two-tailed with the significance level set at α=0.05. Statistical analyses were performed using the R programming language and environment [14].

RESULTS

As previously reported, the median time to progression or death (PFS) was 10.5 months in the SCS group and 10.7 months in the chemotherapy-alone group. Similarly, the median OS was 33.9 months in the SCS group and 33.7 months in the chemotherapy-alone group. The patient characteristics of the 201 patients underwent SCS are listed on Table 1. Ninety-four percent had a performance status of 0–1, 75% were serous histology and 93% were stage III with only 8.5% having grade 1 histology. Among the 201 patients who underwent SCS; 76.1% had a gross PR, 4.0% had a pathologic PR, and 19.9% had a pathologic CR.(Table 2)

The median PFS for patients with a pathologic CR was 16.1 months, pathologic PR was 13.5 months and for gross disease was 11.7 months, p=0.002.(Figure 1) The median OS for patients with a pathologic CR was 51.5 months, pathologic PR was 42.6 months and for gross disease was 34.9 months, p=0.018.(Figure 2)

A pathologic CR was not associated with stage, residual disease diameter, tumor histology or grade, age, baseline CA 125. (Table 3)

DISCUSSION

Surgical assessment of disease extent was first studied by Wangensteen et al in gastrointestinal cancer [15]. Surgical assessment of disease following treatment (second-look laparotomy) was quickly adopted in ovarian cancer due to the toxicity of continued alkylating agent therapy and difficulty of confirming a complete responses to chemotherapy [16,17]. Second-Look laparotomy (SLL) became an NCI standard over 3 decades for evaluating patients in a complete clinical response following the completion of chemotherapy. In both GOG-104 and GOG-172 intraperitoneal therapy was associated with increased rates of negative SLL and corresponding increase in survival [18,19]. In GOG-158, a trial which established equivalence of two platinum compounds; cisplatin or carboplatin with paclitaxel, SLL was optional but had to be pre-assigned prior to randomization [20]. Second-look laparotomy was not randomly assigned and evaluating the role of SLL was not an objective of the study. However, in an exploratory date analysis, among the 792 patients in the trial 393 underwent SLL and 399 were observed, SLL resulted in a one month improvement in PFS which was non-significant and an identical OS. In view of the lack of benefit and potential for morbidity routine use of SLL was abandoned.

In our study patients with suboptimal disease following primary cytoreductive surgery who had a pathologic CR at secondary cytoreductive surgery had improved PFS and OS. The outcome of patients who achieved a pathologic PR was only marginally better than those with a gross PR both of which were significantly worse than a pathologic CR. This is consistent with our extensive experience with SLL and the Italian neoadjuvant trial [6,21]. Unfortunately, normal CA 125 values and CT or PET/CT imaging are necessary but not sufficient to ensure a pathologic complete response. Despite normal CA 125 values and

PET/CT scans 55% of patients with advanced stage ovarian cancer have persistent disease at SLL [22].

The use of neoadjuvant chemotherapy as a primary treatment strategy is increasing. At National Comprehensive Cancer Network institutions the use of neoadjuvant chemotherapy has increased and is being utilized in 53% of stage IIIC and 58% of stage IV patients [23]. However, primary debulking surgery has been the primary treatment paradigm utilized by the GOG since its inception. Only one protocol (GOG- 273), which was a protocol designed for elderly patients greater than 70 years of age, allowed neoadjuvant chemotherapy patients to be eligible.[24] This trial did not require interval debulking. Secondary cytoreductive surgery has only been studied in one GOG trial (GOG-152).[10] This allowed us to evaluate the pathologic CR rate following three cycles of chemotherapy. However, one GOG trial in optimal disease stage III patients (GOG-8812) utilized surgical reassessment after three cycles of chemotherapy with cisplatin and cyclophosphamide followed by hyperfractionated abdominal radiotherapy with a pathologic CR rate of 32% [25].

The pathologic complete response rates from induction chemotherapy in patients with optimal primary cytoreductive surgery, suboptimal primary cytoreductive surgery, and neoadjuvant chemotherapy were 32%, 20% and 6% and 4% respectively [25,10,6,7]. This suggests that the amount of residual disease prior to initiation of chemotherapy is related to the pathologic complete response rate. However, in the current study, tumor size was not related to pathologic CR. Similarly, in breast cancer tumor size has not predicted pathologic CR but molecular subgrouping did [26]. Molecular profiling has not been performed in the GOG, Chorus or Italian ovarian cancer studies previously discussed. In ovarian cancer, BRCA germ-line mutation identifies a sub group of patients with deficiencies in homologous re-combination DNA repair and improved response to chemotherapy and longer progression free and overall survival.[27] In a recent study of neoadjuvant chemotherapy in breast cancer, patients who had deficiencies in homologous re-combination DNA repair had a significantly higher rate of pathologicCR 58% versus 18%.[28] It is likely molecular profiling of ovarian cancer patients will identify a subgroup of patients who are more likely to have a complete pathologic response.

The strengths of this study include; uniform chemotherapy treatment and uniform timing of surgical disease reassessment. Additionally, this is a multi-centered prospective clinical trial with a large number of patients with longitudinal follow-up. However, weaknesses of this study include; the lack of genetic testing for germ-line BRCA and BRCAoid mutations and the lack of tumor profiling. The GOG did establish a prospective tumor protocol (GOG-136) in 1992, however only 11% of GOG-152 patients had banked tissue.

Based on the results of GOG-152, secondary cytoreductive surgery following suboptimal tumor resection by a gynecologic oncologist is not standard of care. But, the findings of this study are thought provoking and confirm the previously reported retrospective data following neoadjuvant chemotherapy where a pathologic complete response is associated with improved survival. Surgical intervention following neoadjuvant chemotherapy (interval debulking surgery) is an accepted treatment paradigm. Therefore, if the pathologic response rates following neoadjuvant can be confirmed, neoadjuvant chemotherapy followed by early

surgical reassessment may be a new platform for accelerated oncology therapeutic approval in ovarian cancer. Future NRG studies are evaluating novel agents in combination with platinum and taxane based regimens to see if the addition of novel therapeutic agents will increase of pathologic complete response and improve survival outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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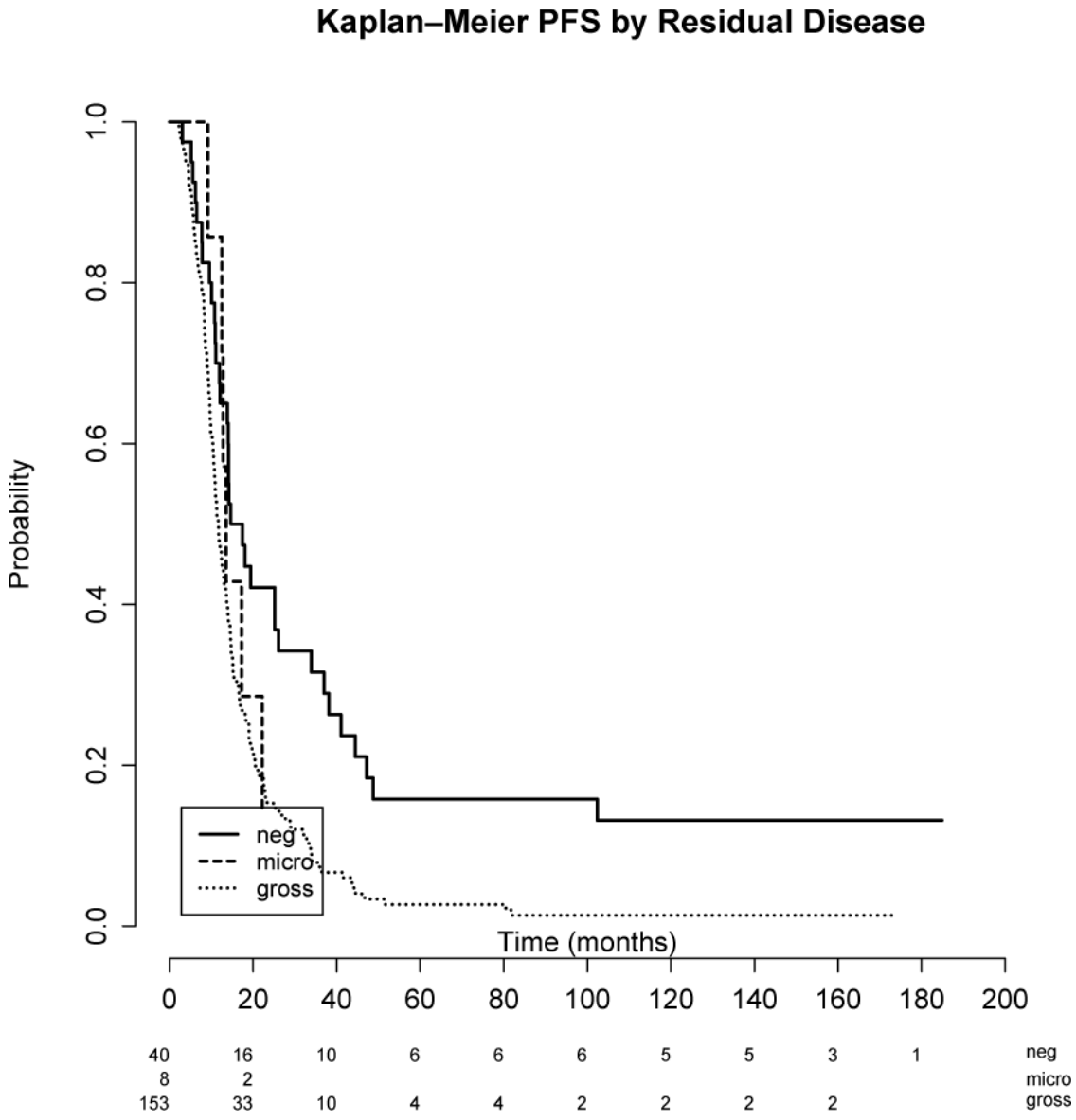

Figure 1.
Kaplan-Meier PFS by Residual Disease

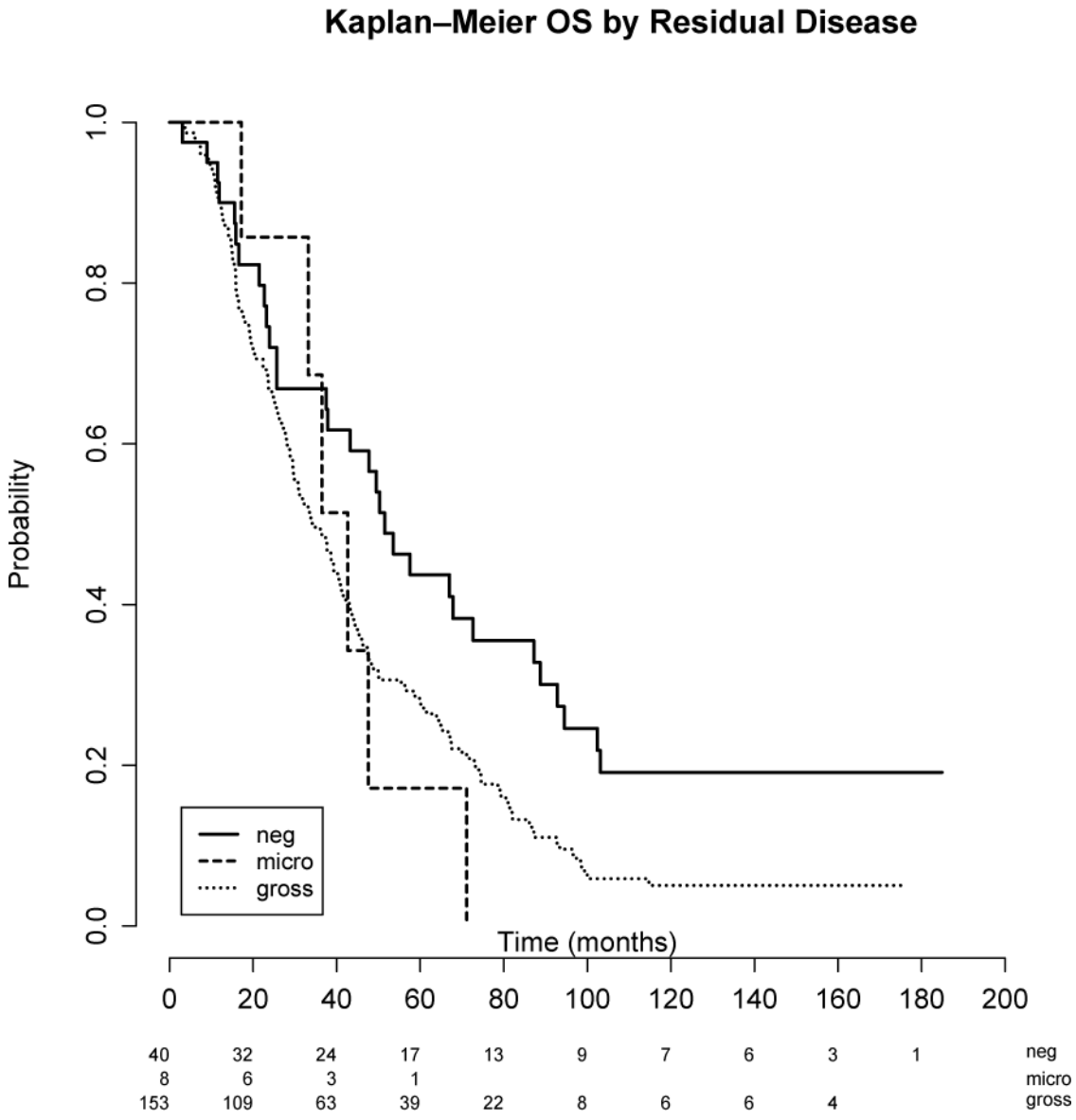

Figure 2.
Kaplan-Meier OS by Residual Disease

Table 1

Patient Characteristics

	N	
Age years	201	49.9 57.6 65.3
Performance status	201	
0		38.3% (77)
1		55.7% (112)
2		6.0% (12)
Histology	201	
serous		75.6% (152)
mixed epithelial		9.5% (19)
endometrioid		8.5% (17)
other		6.5% (13)
Top-level FIGO stage	201	
III		92.5% (186)
IV		7.5% (15)
Tumor grade (differentiation)	201	
Grade 1		8.5% (17)
Grade 2		38.8% (78)
Grade 3		52.2% (105)
NA		0.5% (1)
Pre-study residual cm	193	10 15 20
Baseline CA-125 IU/ml	159	145 335 858

a b c represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables.

N is the number of non–missing values. Numbers after percents are frequencies.

Table 2

Findings at IDS; 201 patients

Findings	Number (%)
Gross residual disease	153 (76.1%)
No gross residual disease but microscopic disease	8 (4.0%)
No gross residual disease and no microscopic disease.	40 (19.9%)
TOTAL	216 (100%)

Table 3

Patient Characteristics by Response (*N* = 201)

	N	neg	micro	gross	Test Statistic
		***N* = 40**	***N* = 8**	***N* = 153**	
Age years	201	51.8 58.4 65.8	60.1 63.1 66.7	49.4 56.6 64.8	*P* = 0.171[1]
Histology	201				*P* = 0.745[2]
serous		77.5% (31)	75.0% (6)	75.2% (115)	
mixed epithelial		5.0% (2)	12.5% (1)	10.5% (16)	
endometrioid		7.5% (3)	0.0% (0)	9.2% (14)	
other		10.0% (4)	12.5% (1)	5.2% (8)	
Top-level FIGO stage	201				*P* = 0.596[2]
III		90.0% (36)	100.0% (8)	92.8% (142)	
IV		10.0% (4)	0.0% (0)	7.2% (11)	
Tumor grade	200				*P* = 0.655[2]
Grade 1		5.0% (2)	0.0% (0)	9.8% (15)	
Grade 2		42.5% (17)	57.1% (4)	37.3% (57)	
Grade 3		52.5% (21)	42.9% (3)	52.9% (81)	
Residual disease[3]	193	10.00 17.50 20.00	5.75 10.00 14.75	10.00 15.00 20.00	*P* = 0.213[1]
Baseline CA-125	159	229.8 444.0 844.2	87.5 153.0 400.9	132.9 317.5 981.0	*P* = 0.267[1]

a b c represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables.

N is the number of non–missing values.

Numbers after percents are frequencies. Tests used:

[1] Kruskal-Wallis test;

[2] Pearson test,

[3] Residual disease following primary surgery